REMARKS

Reconsideration and withdrawal of the rejections set forth in the Office action dated March 28, 2001 are respectfully requested.

Applicants petition the Commissioner for a 2-month extension of time. A separate petition accompanies this amendment.

Attached hereto is a marked-up version of the changes made to the specification and claims. The attached pages are captioned **"Version with markings to show changes made."**

I. Amendments

The specification has been amended to correct obvious typographical errors.

Claim 1 has been amended to recite that the step of administering the conjugate to a multi-drug resistant cell is effective to achieve accumulation of the drug in the cell. Basis for the recitation of a multi-drug resistant cell is found, for example, on page 5, line 27. Basis for the recitation of that administering is effective to achieve accumulation of the drug in the cell is found, for example, on page 6, lines 3-5.

The claim amendments add no new matter.

II. Rejections under 35 U.S.C. §102

Claims 1-2 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Mislick *et al.* (*Bioconjugate Chem.*, 6:512-515 (1995)).

Claims 1-2, 4-14, and 16-21 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Lee *et al.* (*Biochimica et Biophysica Acta*, 1233:134-144 (1995)).

Claims 1-2, 4-14, and 16-21 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Goren *et al.* (*Proceed. Intl. Sump. Control Rel. Bioact. Mater.*, 24:865-866 (1997)) or

Horowitz *et al.* (Chemistry and Biology of Pteridines and Folates, Pfleiderer and Rokos, eds., 11th Symposium, p. 353-356 Berlin, 1997).

Claims 1-3 and 13-15 were rejected under 35 U.S.C. §102(a) as allegedly anticipated by Brasier (U.S. Patent No. 5,804,445).

These rejections are respectfully traversed for the following reasons.

A. The Invention

The present invention relates to a method of administering a therapeutic compound to a multi-drug resistant (MDR) cell expressing P-glycoprotein. The method includes

(1) preparing a conjugate composed of (i) a carrier; (ii) a folate ligand attached to the carrier; and (iii) a therapeutic agent associated with the carrier; and

(2) administering the conjugate to a subject;

(3) whereby said administering is effective to achieve accumulation of the therapeutic agent in the cell.

In another aspect, the invention relates to a composition for delivery of a compound to an MDR cell (claims 13-21). The composition is comprised of:

(1) a carrier molecule;

(2) at least one folate ligand attached to the carrier molecule; and

(3) a therapeutic compound associated with the carrier,

(4) wherein the composition is effective to achieve accumulation of the therapeutic compound in the cell in an amount sufficient to be cytotoxic.

B. The Cited Art

MISLICK *ET AL.* relate to the intracellular delivery of DNA by folate receptor endocytosis. Folate is attached to polylysine and complexed with DNA.

Mislick *et al.* fail to show or suggest a method for achieving accumulation of a drug in MDR cells. Mislick *et al.* also fail to show or suggest that accumulation of the folate-targeted compound in an MDR cell is achieved.

LEE *ET AL.* relate to targeting doxorubicin to cancer cells overexpressing the folic acid membrane-associated receptor by entrapping doxorubicin in folate-targeted liposomes.

Lee *et al.* fail to show or suggest a method for achieving accumulation of a drug in MDR cells. Lee *et al.* also fail to show or suggest that accumulation of the folate-targeted compound in an MDR cell is achieved.

GOREN *ET AL.* relate to folate-targeted liposomes for tumor targeting.

Goren *et al.* fail to show or suggest a method for achieving accumulation of a drug in MDR cells. Goren *et al.* also fail to show or suggest that accumulation of the folate-targeted compound in an MDR cell is achieved.

HOROWITZ *ET AL.* relate to the cytotoxicity and binding of folic acid-targeted liposomes.

Horowitz *et al.* fail to show or suggest a method for achieving accumulation of a drug in MDR cells. Horowitz *et al.* also fail to show or suggest that accumulation of the folate-targeted compound in an MDR cell is achieved.

BRASIER relates to asthma treatment by administering a polypeptide comprising a NF-IL6 tryptic core domain in combination with a excipient, diluent or carrier which may be folate-conjugated bovine serum albumin or a liposome.

Brasier fails to teach or suggest a method for achieving accumulation of a drug in MDR cells. Brasier also fails to show or suggest that accumulation of the folate-targeted compound in an MDR cell is achieved.

C. Analysis

1. Legal Standard for Novelty

The standard for lack of novelty, that is, for anticipation, is one of strict identity. To anticipate a claim for a patent, a single prior source must contain all its essential elements. M.P.E.P. § 2131

2. Rejection over Mislick *et al.*

As noted above, the method of the present invention (claims 1-12) includes the following three elements:

(1) preparing a conjugate composed of (i) a carrier; (ii) a folate ligand attached to the carrier; and (iii) a therapeutic agent associated with the carrier;

(2) administering the conjugate to a subject; and

(3) whereby said administering is effective to achieve accumulation of the therapeutic agent in the cell.

The composition claims of the present invention (claims 13-21) include the following four elements:

(1) a carrier molecule;

(2) at least one folate ligand attached to the carrier molecule; and

(3) a therapeutic compound associated with the carrier,

(4) wherein the composition is effective to achieve accumulation of the therapeutic compound in the cell in an amount sufficient to be cytotoxic.

At a minimum, Mislick *et al.* fail to teach or suggest element (3) of the method claim and element (4) of the composition claims. There is no teaching or suggestion in Mislick *et al.* that administering a folate-targeted drug conjugate would be effective to achieve accumulation of the drug in an MDR cell.

As the standard for novelty has not been satisfied, withdrawal of the rejection under 35 U.S.C. §102 is respectfully requested.

3. Rejection over Lee *et al.*

Lee *et al.* pertain to folate-targeted liposomes for delivery of doxorubicin to epithelial tumor cells. At a minimum, Lee *et al.* fail to teach or suggest element (3) of the method claims and element (4) of the composition claims. There is no teaching or suggestion in Lee *et al.* that administering a folate-targeted drug conjugate would be effective to achieve accumulation of the drug in an MDR cell.

As the standard for novelty has not been satisfied, withdrawal of the rejection under 35 U.S.C. §102 is respectfully requested.

4. Rejection over Goren *et al.* or Horowitz *et al.*

Goren *et al.* pertain to folate targeted liposomes for the delivery of doxorubicin to tumor cells. At a minimum, Goren *et al.* fail to teach or suggest all the elements of the claimed invention. There is no teaching or suggestion in Goren *et al.* that administering a folate-targeted drug conjugate would be effective to achieve accumulation of the drug in an MDR cell.

Similar to Goren *et al.*, Horowitz *et al.* relate to folate-targeted liposomes for delivery to tumors. Horowitz *et al.* fail to teach or suggest element (3) of the claimed invention. There is no teaching or suggestion in Horowitz *et al.* that administering a folate-targeted drug conjugate would be effective to achieve accumulation of the drug in an MDR cell.

As the standard for novelty has not been satisfied, withdrawal of the rejection under 35 U.S.C. §102 is respectfully requested.

5. Rejection over Brasier

Brasier relates to the administration of a polypeptide, and in one embodiment, in combination with a folate-conjugated liposome for the treatment of asthma. At a minimum, Brasier fails to teach or suggest element (3) of the method claims and element (4) of the composition claims. There is simply no teaching in Brasier that administering a folate-targeted drug conjugate would be effective to achieve accumulation of the drug in an MDR cell.

Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §102 in view of Brasier.

III. Rejections under 35 U.S.C. §103

Claims 1-2, 4-14, and 16-21 were rejected under 35 U.S.C. §103 as allegedly obvious over Lee *et al.* or Goren *et al.* or Horowitz *et al.*

Claims 1-3, and 13-16 were rejected under 35 U.S.C. §103 as allegedly obvious over Mislick *et al.* or Brasier in view of Lee *et al.* or Goren *et al.* or Horowitz *et al.* individually or in combination.

These rejections are respectfully traversed.

Summaries of the present invention and of the cited documents are given above.

A. Analysis

As stated in M.P.E.P. § 2143, "to establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art references (or references when combined) must teach or suggest all the claim limitations."

Applicants assert that the cited documents fail to teach of suggest the invention as claimed. More specifically, the cited documents fail to show or suggest, for example, that administering a folate-targeted drug conjugate would be effective to achieve accumulation of the drug in an MDR cell.

1. Rejection over Lee *et al.* or Goren *et al.* or Horowitz *et al.*

The present invention provides, inter alia, accumulation of the drug in the cells upon administration of the folate-targeted drug conjugate.

The cited references fail to teach or suggest this claimed feature. None of the references show or suggest that administering a folated-targeted drug conjugate would be effective to achieve accumulation of the drug in an MDR cell.

Accordingly, as the references either alone or in combination fialt to teach the administration of a folate-targeted drug conjugate would be effective to achieve accumulation of the drug in MDR cells, the invention patentably defines over the cited references.

Moreover, the references are silent on the problem of MDR, and the references either alone or in combination fail to provide a suggestion that administration of a folate-targeted conjugate would accumulate in MDR cells.

Therefore, withdrawal of the rejection under 35 U.S.C. § 103 over Lee *et al.* or Goren *et al.* or Horowitz *et al.* is respectfully requested.

2. Rejection over Mislick *et al.* or Brasier, in view of Lee *et al.* or Goren *et al.* or Horowitz *et al.*

The arguments above directly apply to the rejection over Mislick *et al.* or Brasier, in view of Lee *et al.* or Goren *et al.* or Horowitz *et al.* Namely, none of the references either alone or in combination show or suggest that administering a folate-targeted drug conjugate would achieve accumulation of the drug in an MDR cell.

Mislick *et al.* and Brasier relate to delivery of folate-targeted DNA (Mislick) or polypeptides (Brasier). Neither reference shows or suggests that administering a folate-targeted drug conjugate would achieve accumulation of the drug in an MDR cell.

None of the cited secondary references supplement that which is missing form the primary references. Namely, none of these references show or suggest that administering a folate-targeted drug conjugate would achieve accumulation of the drug in an MDR cell.

Finally, the references provide no guidance in overcoming MDR, as claimed by Applicants.

Accordingly, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §103.

IV. CONCLUSION

In view of the above remarks, Applicants submit that the claims now pending are in condition for allowance. A Notice of Allowance is, therefore, respectfully requested.

The Examiner is invited to contact Applicants' representative at 650-838-4402 if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Cancers which express P-glycoprotein include cancers derived from tissues which normally express the *MDR1* gene, namely cancers of the liver, colon, kidney, pancreas and adrenal. Expression of the gene is also seen during the course of chemotherapy with multidrug-resistant drugs in leukemias, lymphomas, breast and ovarian cancer, and many other cancers. These cancers initially respond to chemotherapy , but when the cancer relapses, the [cnaner] cancer cells frequently express more P-glycoprotein. There are cancers derived from tissues which do not normally express P-glycoprotein but in which P-glycoprotein expression increases during the development of the cancer. One example is chronic myelogenous leukemia, which when it goes into blast crisis, expresses more P-glycoprotein irrespective of the previous treatment history (Gottesman, M.M. *Cancer Research*, 53:747-754 (1993)).

In another aspect, the invention includes a liposome composition for administration of a therapeutic compound to the cytoplasm of a cell characterized by increased expression of the MDR1 gene. The liposomes are composed of vesicle-forming lipids and include[ing] a vesicle forming lipid derivatized with a hydrophilic polymer chain having a free distal end. A folate ligand is attached to the free distal end of at least a portion of the hydrophilic polymer chains, and a therapeutic agent entrapped in the liposomes.

1. (Amended) A method of administering a therapeutic compound to a multi-drug resistant cell expressing P-glycoprotein, comprising

preparing a conjugate composed of (i) a carrier; (ii) a folate ligand attached to the carrier; and (iii) a therapeutic agent associated with the carrier; and

administering the conjugate to a subject;

whereby said administering is effective to achieve accumulation of said therapeutic agent in said cell.